PATENT

Docket No. 1203-48

Commissioner of Patents and Trademarks
Washington, D.C. 20231

NEW APPLICATION TRANSMITTAL

Transmitted herewith for filing is the patent application of
Inventor(s): CHUNG, Kyu-Nung; SHEEN, Yhun-Yhong; SHIN, Hyun-Jong

WARNING: *Patent must be applied for in the name(s) of all of the actual inventor(s). 37 CFR 1.41 and 1.53(b).*

For (title): AN IMPROVED STABLE INJECTION FORMULATION CONTAINING PACLITAXEL

1. Type of Application

This new application is for a(n) (*check one applicable item below*):

- [x] Original
- [ ] Design

WARNING: *Do not use this transmittal for a completion in the U.S. of an International Application under 35 U.S.C. 371(c)(4) unless the International Application is being filed as a divisional, continuation or continuation-in-part application.*

NOTE: *If one of the following 3 items apply then complete and attach ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF A PRIOR U.S. APPLICATION CLAIMED*

- [ ] Divisional
- [ ] Continuation
- [ ] Continuation-in-part (CIP)

2. Benefit of Prior U.S. Application(s) (35 USC 120)

NOTE: *If the new application being transmitted is a divisional, continuation or a continuation-in-part of a parent case, or where the parent case is an International Application which designated the U.S., then check the following item and complete and attach ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED.*

- [ ] The new application being transmitted claims the benefit of prior U.S. application(s) and enclosed are ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED.

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this New Application Transmittal and the documents referred to as enclosed therein are being deposited with the United States Postal Service on this date _____ in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number _____ addressed to the: Commissioner of Patents and Trademarks, Washington, D.C. 20231

John S. Egbert
(Type or print name of person mailing paper)

_____
(Signature of person mailing paper)

NOTE: ***Each*** *paper or fee referred to as enclosed herein has the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 CFR 1.10(b).*

3. Papers Enclosed Which Are Required For Filing Date Under 37 CFR 1.53(b) (Regular) or 37 CFR 1.153 (Design) Application

11 Pages of specification

1 Pages of claims

1 Pages of Abstract

0 Sheets of drawing

- ☐ formal
- ☒ informal
  - ☒ in triplicate

NOTE: The Notice of October 7, 1985 (1059 O.G. 38-39) states the following: "Submission of Drawings —For your convenience and for more effective handling of any drawing corrections which may be necessary, please DO NOT SUBMIT ORIGINAL DRAWINGS WITH PATENT APPLICATIONS. DO SUBMIT THREE HIGH QUALITY COPIES. If the copies submitted pass the formality review and patent examination, no substitute drawings will be necessary. If corrections are necessary, they should be made to the original drawings. Either a good copy of the corrected drawings or the corrected original can then be submitted after the Notice of Allowability is mailed." The Notice of November 25, 1985 (1061 O.G. 12) further clarifies the submission of drawing practice by pointing out that the copies that are submitted to the office must be on strong, white, smooth and non-shiny paper and also points out that drawings for patent applications do not need to be submitted on bristol board.

4. Additional papers enclosed

- ☒ Preliminary Amendment
- ☐ Information Disclosure Statement
- ☐ Form PTO-1449
- ☐ Citations
- ☐ Declaration of Biological Deposit
- ☐ Special Comments
- ☐ Other

5. Declaration or oath

☒ Enclosed

executed by *(check all applicable boxes)*

- ☒ inventor(s).
- ☐ legal representative of inventor(s). 37 CFR 1.42 or 1.43
- ☐ joint inventor or person showing a proprietary interest on behalf of inventor who refused to sign or cannot be reached.

☐ this is the petition required by 37 CFR 1.47 and the statement required by 37 CFR 1.47 is also attached. *See item 12 below for fee.*

☐ Not Enclosed.

WARNING: Where the filing is a completion in the U.S. of an International Application but where a declaration is not available or where the completion of the U.S. application contains subject matter in addition to the International Application the application may be treated as a continuation or continuation-in-part, as the case may be, utilizing ADDED PAGE FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION CLAIMED.

☐ Application is made by a person authorized under 37 CFR 1.41(c) on behalf of *all* the above named inventor(s). The declaration or oath, along with the surcharge required by 37 CFR 1.16(e) can be filed subsequently.

WARNING: It is important that all the correct inventor(s) are named for filing under 37 CFR 1.41(c) and 1.53(b).

☐ Showing that the filing is authorized. (*Not required unless called into question. 37 CFR 1.41(d).*

6. Inventorship Statement

WARNING: If the named inventors are each not the inventors of all the claims an explanation, including the ownership of the various claims at the time the last claimed invention was made, should be submitted.

The inventorship for all the claims in this application are:

☒ The same

or

☐ Are not the same. An explanation, including the ownership of the various claims at the time the last claimed invention was made,

☐ is submitted

☐ will be submitted.

7. Language

NOTE: An application including a signed oath or declaration may be filed in a language other than English. A verified English translation of the non-English language application and the processing fee of $26.00 required by 37 CFR 1.17(k) is required to be filed with the application or within such time as may be set by the Office. 37 CFR 1.52(d).

NOTE: A non-English oath or declaration in the form provided or approved by the PTO need not be translated. 37 CFR 1.69(b).

☒ English

☐ non-English

☐ the attached translation is a verified translation. 37 CFR 1.52(d).

NOTE: 37 CFR 1.52(d) "An application may be filed in a language other than English. A verified English translation of the non-English language application and the fee set forth in § 1.17(k) are required to be filed with the application or within such time as may be set by the Office."

8. Assignment

☒ An assignment of the invention to Kyu-Nung Chung

☒ is attached

☐ will follow

9. Certified Copy

Certified copy(ies) of application(s)

Korea	99-9928	March 23,1999
(country)	(appln no.)	(filed)
(country)	(appln no.)	(filed)
(country)	(appln no.)	(filed)

from which priority is claimed

☒ is(are) attached

☐ will follow

WARNING: The foreign application forming the basis for the claim for priority must be referred to in the oath or declaration. 37 CFR 1.55(a) and 1.63

NOTE: This item is for any foreign priority for which the application being filed directly relates. If any parent U.S. application or International Application from which this application claims benefit under 35 U.S.C. 120 is itself entitled to priority from a prior foreign application then complete item 17 on the ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED.

10. Fee Calculation

A. ☒ Regular application

CLAIMS AS FILED					
Number filed		Number Extra		Rate	Basic Fee 760
Total Claims	4	−20=	X	$ 22.00	
Independent Claims	1	−3=	X	$ 74.00	
Multiple dependent claim(s), if any		0		$230.00	

☐ Amendment cancelling extra claims enclosed

☐ Amendment deleting multiple dependencies enclosed

☐ Fee for extra claims is not being paid at this time

NOTE: If the fees for extra claims are not paid on filing they must be paid or the claims cancelled by amendment, prior to the expiration of the time period set for response by the Patent and Trademark Office in any notice of fee deficiency. 37 CFR 1.16(d)

Filing Fee Calculation $ 760

B. ☐ Design application ($290.00—37 CFR 1.16(f))

Filing Fee Calculation $ _____

11. Small Entity Statement(s)

☒ Verified Statement(s) that this is a filing by a small entity under 37 CFR 1.9 and 1.27 is(are) attached.

Filing Fee Calculation (50% of A or B above) $ 380

NOTE Any excess of the full fee paid will be refunded if a verified statement and a refund request are filed within 2 months of the date of timely payment of a full fee. 37 CFR 1.28(a)

12. Fee Payment Being Made At This Time

☐ Not Enclosed

☐ No filing fee is to be paid at this time. (*This and the surcharge required by 37 CFR 1.16(e) can be paid subsequently.*)

☒ Enclosed

☒ basic filing fee $ 380

☒ recording assignment - $40.00 (37 CFR 1.21(h)(1)) 40 $

☐ petition fee for filing by other than all the inventors or person on behalf of the inventor where inventor refused to sign or cannot be reached. ($140.00; 37 CFR 1.47 and 1.17(h)) $

☐ for processing an application with a specification in a non-English language. ($26.00; 37 CFR 1.52(d) and 1.17(k) $

☐ processing and retention fee ($100.00; 37 CFR 1.53(d) and 1.21(l)) $

NOTE: 37 CFR 1.21(l) establishes a fee for processing and retaining any application which is abandoned for failing to complete the application pursuant to 37 CFR 1.53(d) and this, as well as the changes to 37 CFR 1.53 and 1.78, indicate that in order to obtain the benefit of a prior U.S. application, either the basic filing fee must be paid or the processing and retention fee of § 1.21(l) must be paid within 1 year from notification under § 53(d).

Total fees enclosed $ 420

13. Method of Payment of Fees

☒ check in the amount of $ 380 + 40

☐ charge Account No. _____ in the amount of $_____. A duplicate of this transmittal is attached.

NOTE: Fees should be itemized in such a manner that it is clear for which purpose the fees are paid. 37 CFR 1.22(b).

14. Authorization to Charge Additional Fees

WARNING: If no fees are to be paid on filing the following items should not be completed.

WARNING: Accurately count claims, especially multiple dependent claims, to avoid unexpected high charges, if extra claim charges are authorized.

☒ The Commissioner is hereby authorized to charge the following additional fees by this paper and during the entire pendency of this application to Account No. 08-0879 :

☒ 37 CFR 1.16 (filing fees)

☐ 37 CFR 1.16 (presentation of extra claims)

NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 CFR 1.16(d)), it might be best not to authorize the PTO to charge additional claim fees, except possibly when dealing with amendments after final action.

☐ 37 CFR 1.16(e) (surcharge for filing the basic filing fee and/or declaration on a date later than the filing date of the application)

☐ 37 CFR 1.17 (application processing fees)

WARNING. *While 37 CFR 1.17(a), (b), (c) and (d) deal with extensions of time under § 1.136(a) this authorization should be made only with the knowledge that "Submission of the appropriate extension fee under 37 C.F.R. 1.136(a) is to be made unless a request or petition for extension is filed." (Emphasis added) Notice of November 5, 1985 (1060 O.G. 27)*

☐ 37 CFR 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 CFR 1.311(b)

NOTE *Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance 37 CFR 1.311(b)*

NOTE *37 CFR 1.28(b) requires "Notification of any change in loss of entitlement to small entity status must be filed in the application . . . prior to paying, or at the time of paying, . . . issue fee" From the wording of 37 CFR 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.*

15. Instructions As To Overpayment

☒ credit Account No 08-0879

☐ refund

Reg. No. 30,627

Tel. No. (713) 223-4034

SIGNATURE OF ATTORNEY

John S. Egbert

Type or print name of attorney

1018 Preston, Suite 100

P.O. Address

Houston, Texas 77002

☐ **Incorporation by reference of added pages**

Check the following item if the application in this transmittal claims the benefit of prior U.S. application(s) (including an international application entering the U.S. stage as a continuation, divisional or C-I-P application) and complete and attach the ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED

☐ Plus Added Pages For New Application Transmittal Where Benefit Of Prior U.S. Application(s) Claimed

Number of pages added _____

☐ Plus Added Pages For Papers Referred To In Item 4 Above

Number of pages added _____

☒ **Statement Where No Further Pages Added**

If no further pages form a part of this Transmittal then end this Transmittal with this page and check the following item

☒ This transmittal ends with this page.

(2-92)

VERIFIED STATEMENT CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) & 1.27(c))–SMALL BUSINESS CONCERN

Docket Number (Optional)
1203-48

Applicant or Patentee: CHUNG, Kyu-Nung; SHEEN, Yhun-Yhong; SHIN, Hyun-Jong
Serial or Patent No.: _____
Filed or Issued: _____
Title: AN IMPROVED STABLE INJECTION FORMULATION CONTAINING PACLITAXEL

I hereby declare that I am

- ☐ the owner of the small business concern identified below:
- ☒ an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF SMALL BUSINESS CONCERN Kyu-Nung Chung
ADDRESS OF SMALL BUSINESS CONCERN Samick APT 2-205, #1681 SeoCho-Dong SeoCho-Ku, Seoul Korea

I hereby declare that the above identified small business concern qualifies as a small business concern as defined in 13 CFR 121.12, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees to the United States Patent and Trademark Office, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention described in:

- ☐ the specification filed herewith with title as listed above.
- ☒ the application identified above.
- ☐ the patent identified above.

If the rights held by the above identified small business concern are not exclusive, each individual, concern or organization having rights in the invention must file separate verified statements averring to their status as small entities, and no rights to the invention are held by any person, other than the inventor, who would not qualify as an independent inventor under 37 CFR 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d), or a nonprofit organization under 37 CFR 1.9(e).

Each person, concern or organization having any rights in the invention is listed below:

- ☒ no such person, concern, or organization exists.
- ☐ each such person, concern or organization is listed below.

Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING Kyu-Nung Chung

TITLE OF PERSON IF OTHER THAN OWNER _____

ADDRESS OF PERSON SIGNING Samick APT 2-205, #1681 SeoCho-Dong, SeoCho-Ku Seoul Korea

SIGNATURE K N Chung DATE 09/06/1999

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: CHUNG; Kyu-Nung; SHEEN, Yhun-Yhong; SHIN, Jyun-Jong

SERIAL NO.:

FILED: Herewith

TITLE: AN IMPROVED STABLE INJECTION FORMULATION CONTAINING PACLITAXEL

PRELIMINARY AMENDMENT

Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

In conjunction with the filing of the present application, and prior to an initial Official Action on this matter, please amend the above-identified application as follows:

IN THE TITLE

On page 1, line 1, delete "IMPROVED," and insert therefor --IMPROVED--.

IN THE SPECIFICATION

On page 1, line 7, delete "improved," and insert therefor --stable--.

On page 1, lines 19, delete "has the limitation on" and insert therefor --is limited in--.

On page 1, line 21, delete "sold" and insert therefor --, sold--.

On page 1, line 21, delete "which".

On page 1, line 22, delete "paclitaxel," and insert therefor --paclitaxel and--.

On page 1, line 24, delete "the side" and insert therefor --a--.

On page 1, line 24, delete "as the" and insert therefor --as a--.

On page 2, line 14, delete "one".

On page 3, line 3, delete "We have made a ceaseless effort to find" and insert therefor --Extensive efforts have been taken to develop--.

On page 3, line 6, delete "formulation" and insert therefor --formulations--.

On page 3, lines 6-7, delete "we have found" and insert therefor --it has been determined--.

On page 3, line 9, delete before "compared" insert --when--.

On page 3, line 13, delete "we found" and insert therefor --it has been determined--.

On page 3, line 14, delete "which has" and insert therefor --having--.

On page 4, line 18, delete "obvious" and insert therefor --clear--.

On page 5, lines 20-21, delete "the method" and insert therefor --methods--.

On page 6, line 1, delete "we added".

On page 6, line 2, delete "hrs" and insert therefor --hours--.

On page 6, line 14, delete "improved," and insert therefor --stable--.

On page 7, line 4, delete "we have attempted" and insert therefor --it was necessary--.

On page 7, line 7, delete "Our successful attempt has included utilization of" and insert therefor --The present invention utilizes--.

On page 11, lines 9-11, delete "In the case of rabbits, the toxicology study is being continued at the moment. Final result will be shown soon.".

IN THE CLAIMS

On page 12, line 1, delete "WHAT IS CLAIMED IS" and insert therefor

--CLAIMS

We Claim:--.

IN THE ABSTRACT

On page 13, line 3, delete "Disclosed herein is an" and insert therefor --An--.

On page 13, line 3, delete "improved," and insert therefor --stable--.

On page 13, line 4, delete "formulation. The formulation comprises" and insert therefor --formulation having--.

On page 13, line 8, after "all over the world." insert --The formulation includes paclitaxel 30 mg, povidone 80 mg, oxyethylene sorbitol oleate 0.5 to 2.0 ml, $(oxyethylene\ glycol)_{15\text{-}20}$ fatty acid monoester 0.5 to 2.0 ml, polyethylene glycol 1.0 ml, and anhydrous alcohol 2.0 ml. The oxyethylene sorbitol oleate is either $(oxyethylene)_{60}$ sorbitol tetraoleate or $(oxyehtylene)_{45}$ sorbitol trioleate.--.

REMARKS

The present Preliminary Amendment has been entered for the purpose of placing the application into a more proper U.S. format. In particular, certain grammatical and idiomatic inconsistencies have been corrected by amendment to the specification.

The Abstract has been amended so as to conform with U.S. requirements.

Applicant respectfully requests that the present Amendment be entered prior to an initial

Official Action on the present application.

Respectfully submitted,

9-16-99

Date

John S. Egbert
Reg. No. 30,627
Attorney for Applicant

Harrison & Egbert
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Houston, Texas 77002
(713)223-4034

AN IMPROVED, STABLE INJECTION FORMULATION CONTAINING PACLITAXEL.

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to an improved, stable injection formulation containing paclitaxel.

Description of the Prior Art

Paclitaxel is a diterpenoid compound which is widely used as an antineoplastic agent for the treatment of the breast and ovarian cancers. Also, the clinical tests of the paclitaxel for the other kinds of cancers are presently carried out in several countries. However, because of the extraordinary low solubility of the paclitaxel in water and in the pharmaceutically acceptable solvents (see, Flora K.P. et al, NCI Investigational Drugs Chemical Information, NCI, pp218(1992), the paclitaxel has the limitation on its formulation.

Cremophor EL sold by BASF, which is typically used as a solubilizer for the paclitaxel, is a condensation product of ethylene oxide and castor oil. This solubilizer is known to cause the side reaction, such as the hyperallergic side reaction, when administered to patients. See, Alka-On Yuksel.

H., et al, Pharmaceutical Research 11, 206(1994). Moreover, the injection formulation containing such a solubilizer has less dilution stability, when the formulation is diluted with saline or an aqueous dextrose solution. See, Mead Johnson Oncology (1993). The paclitaxel injection formulation exhibits instability over extended periods of time if an adequate pretreatment of the solubilizer is not foreseen. See, USP No. 5,504,102. A specially designed in-filter-infusion system is thus recommended for the administration of the injection formulation. See, Mead Johnson Oncology (1993).

Meanwhile, the commercial formulation presently available contains paclitaxel 30mg/1vial(5ml), Cremophor EL 35.527 mg/ml and anhydrous ethanol 49.7 vol%.

As a result, although the paclitaxel is one among the antineoplastic agents which are most widely used as the injection formulation, it has very low solubility in water or other solvents. Therefore, the solubilizers capable of being used for formulating the paclitaxel into the injection formulation are very limited.

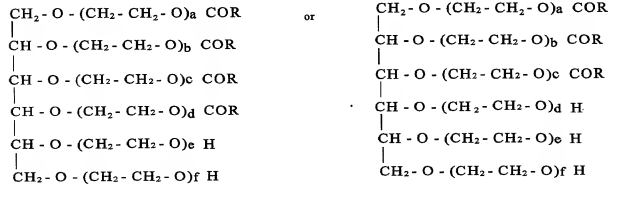
SUMMARY OF THE INVENTION

It is an object of this invention to provide a paclitaxel injection formulation which has improved stability and also less toxicity compared to the presently known paclitaxel

injection formulation containing polyethoxylated castor oil as the solubilizer for the paclitaxel.

We have made a ceaseless effort to find an improved paclitaxel injection formulation having less toxicity, greater stability of dilution, and greater shelf life compared to the presently known formulation. As a result of that, we have found that an ethylene oxide addition product of palm olein-derived oleic acid is advantageous in view of the toxicity and also the stability compared to the ethylene oxide adduct of castor oil, and thus have accomplished this invention.

Starting from the palm olein-derived oleic acid as the lipophilic component instead of castor oil, adjusting the addition ratios of ethylene oxide to sorbitan oleate, we found that polyethoxylated sorbitol oleic polyester which has the following chemical structure provides the most suitable injection formulation:



]where a+b+c+d+e+f are the number of the total ethylene oxide addition moles and n is the degree of the carboxylate esterification in moles.

The polyethoxylated sorbitol oleic polyester of the above formula is already well-known in the cosmetic and surfactant industries and are known to have very mild toxicity. See, Kao's Technical Brochure(1998). There are several manufacturers of such a substance in various countries. The polyethoxylated sorbitol oleic polyester is solidified at a temperature below 10°C. This fact restricts partly the use of this substance as the solubilizer for the paclitaxel even if the use of the anhydrous ethanol as co-solubilizer partially prevents the solidification.

Further elaborate trials with polyethylene glycol mono fatty acid ester together with the polyesters result in the formulation showing good applicability at low temperatures and the desirable extended stability upon dilution with saline or dextrose injections. The obvious criterion for the suitability of the polyethoxylated oleic polyester as the main solubilizer and polyethylene glycol mono fatty acid ester as the auxiliary solubilizer is in that these solubilizers exhibit good solubility in water and in anhydrous alcohol. Another criterion is in that the combined main and auxiliary solubilizers stay in fluid phase even at low temperatures.

It is empirically certain that the HLB value of the

solubilizers which meet the criteria should be as high as 15 but not less than 13. Actually, we have found that all the tried polyoxyethylene sorbitol polyoleate combined with the polyethylene glycol mono fatty acid ester, which provides the desired formulation, have the HLB value of between 13.5 and 15.

Among the numerous polyethoxylated sorbitol oleic polyesters, it is believed that the poly(ethoxylated)$_{30-60}$ sorbitol poly(oleate)$_{2-4}$ is found to give good results. The auxiliary solubilizer suitable for use in this invention includes, for example, poly(oxyethylene)$_{15-20}$ mono oleate, poly(oxyethylene)$_{15-20}$ mono 12-hydroxy stearate and poly(oxyethylene)$_{15-20}$ mono ricinoleate. Moreover, polyethylene glycol mono fatty acid ester of other fatty acid could be used so long as the HLB value of the mono ester lies in the 13.5 to 15.0.

The polyoxyethylene sorbitol oleic polyester can be produced by the method well known in the art or obtained from various suppliers, for example, Kao Corp., Japan. Most of the polyethylene glycol mono fatty acid esters are produced by the method well known in the art or obtained from various suppliers, for example, Sanyo Surfactant Co., Japan. When the adjustment work of the ethylene oxide addition is necessary, it can be done in accordance with the methods known in the art.

In the actual experimental formulations, we added two other components, such as polyethylene glycol and polyvinyl pyrrolidone, to the combined solubilizer, to achieve the quick dispersion of the paclitaxel and also to achieve the extended stability of the formulation up to 5 days. As for maintaining the dilution stability up to 30 hrs, the two additional components are not necessary.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention is an improved formulation containing paclitaxel. This formulation has greater stability and maintains solubility for an extended period of time in solution. Further, the improved, stable formulation showed less toxicity in animal toxicological studies. This is partially due to good compatibility of the oleic acid derivative with animal cells and the low toxic nature of the ester linkages found in the solubilizer.

As described above, paclitaxel is very insoluble in an aqueous medium. Consequently, the commercial injection is formulated as a concentrate at 6mg/ml in a solvent mixture of 50:50 by volume of Cremophor EL and dehydrated alcohol. For the administration, the formulation is admixed in a 5% dextrose injection or a 0.9% sodium chloride injection to a concentration between 0.3 and 1.2mg/ml. As discussed in the

literature, the stability of the commercial paclitaxel is 1 to 2 days, which is not long enough for the continued parenteral administration.

Consequently, we have attempted to develop a novel formulation of paclitaxel designed to keep the paclitaxel dispersed for a minimum of 3 days either in saline or dextrose injections. Our successful attempt has included utilization of the polyoxyethylene sorbitol oleic polyester dissolved in the specific polyethylene glycol mono fatty acid ester admixed with additional components, such as polyethylene glycol as a solvent and polyvinyl pyrrolidone as an accepted dispersant for injection use.

Presented in table I are representative paclitaxel formulations of the present invention.

Table 1

Formulation of the paclitaxel

	1	2	3	4	5	6
Paclitaxel	30mg	30mg	30mg	30mg	30mg	30mg
Povidone K-12	80mg	80mg	80mg	80mg	80mg	80mg
Anhydrous ethanol	1.5ml	1.5ml	1.5ml	1.5ml	1.5ml	1.5ml
PEG 300/400	1.5ml	1.5ml	1.5ml	1.5ml	1.5ml	1.5ml
Poly(oxyethylene)$_{60}$sorbitol tetraoleate	1.0ml	1.0ml	1.0ml	0.5ml	0.5ml	0.5ml
Poly(oxyethylene)$_{15-20}$ mono oleate	1.0ml	-	-	1.5ml	-	-
Poly(oxyethylene)$_{15-20}$ mono 12-hydroxy stearate	-	1.0ml	-	-	1.5ml	-

Poly(oxyethylene)$_{15-20}$mono ricinolate	-	-	1.0ml	-	-	1.5ml

* Other combinations of poly(oxyethylene)$_{30-60}$ sorbitol(oleate)$_{2-4}$ with the above mentioned polyethylene glycol(peg) fatty acid mono ester were formulated, but omitted in table 1 for the simplicity.

The typical procedure to prepare the formulation is the same as that of the commercial formulation using Cremophor El. First, the polyoxyethylene sorbitol polyoleate is heated and mixed with polyethylene glycol mono fatty acid ester and polyethylene glycol to obtain a solubilizer mixture. Paclitaxel is dissolved in anhydrous ethanol with povidone as a dispersant and added portionwise to the solubilizer mixture and homogenized. After complete dissolution, the whole solution is filtered through a 0.2 μ filter and packed in vials under the nitrogen flux. The paclitaxel used is obtained from Bolak Co.,Ltd., Korea and is known to be a purification from taxus cuspidate shootings. Its assay revealed a purity of 99.3% by HPLC.

All the solubilizers were incorporated into the formulation as such from the manufacturers, analyzed and checked for the acid and the hydroxyl value to ensure the minimum existence of the residual reactants. Additionally the heavy metallic and the arsenic levels were checked. Both the anhydrous ethanol and polyethylene glycol 300/400 were pharmaceutical grades. Povidone K-12 was from BASF. Other

polyvinyl pyrrolidone of a different K-value could be used.

The following examples are for illustration purposes only and in no way limit the scope of this invention.

Example 1

Evaluation of the stability of the injection concentrate

Samples of the formulations 1, 2 and 3 listed in Table I were placed in 5ml vials stopped with a Teflon-coated stopper, and put at room temperature(20°C) and at a temperature of 37°C. The sample were withdrawn at 1,2,4 and 6 months and analyzed by HPLC. The results were shown in Table 2.

Table 2

	Formulation 1		Formulation 2		Formulation 3	
Month	Room Temp (20°C)	37°C	Room Temp (20°C)	37°C	Room Temp (20°C)	37°C
0	100.8		100.6		100.4	
1	100.52	100.2	100.6	100.7	100.2	100.5
2	99.85	99.7	99.7	99.6	99.5	99.8
4	99.26	99.5	99.5	99.3	99.2	99.4
6	98.82	99.2	99.1	98.6	99.1	99.0

In all the formulations the change of the paclitaxel content was less than 1.5% after 6 months.

Example 2

Evaluation of the stability of the injection concentrate in solution

Stock solutions in accordance with the formulations 1, 2, 3, 4, 5 and 6 were diluted at ratios of 1:10 and 1:50 in 0.9% sodium chloride solution to give the paclitaxel concentrations of 0.6 and 0.12mg/ml. The solutions were checked at 1, 5, 10, 24, 48, and 72 hours for the sign of precipitation and cloudiness. In all the formulations, the solution of 1:10 and 1:50 showed no signs of precipitation before 72 hours. In the formulations 4,5 and 6, the stability of dilution exceeded more than 5 days.

Example 3

Toxicology study of the solubilizers

In the embodiments of the invention, various combinations of polyoxyethylene sorbitol polyoleate and polyethylene glycol mono fatty acid ester could be used. Also, the mixing ratios of the main and auxiliary solubilizers could be varied.

To get typical toxicological data of the solubilizer combinations, the 50:50% mixture of the poly(oxyethylene)60 sorbitol tetraoleate with poly(oxyethylene) 15 to 20

monooleate was chosen for the intravenous injection of the solubilizer. The results were reported in Final Report on Stability and Toxicology Study for a New Micellar Solubilizer for Injectable Anticancer Agent, May 1999, Research Institute of Pharmacology, Ewha College of Pharmacy, Cosponsored by Ministry of Health and Welfare Korea and Taxon Biotech. Co. When LD_{50} of the combined solubilizers was compared to that of Cremophor EL, LD_{50} of the former was 3 times higher than that of the latter in the male and female rats. In the case of rabbits, the toxicology study is being continued at the moment. Final result will be shown soon.

Although the preferred embodiments of the invention have been disclosed for illustrative purposes, those skilled in the art will appreciate that various modifications, additions and substitutions are possible, without departing from the scope and spirit of the invention as disclosed in the accompanying claims.

WHAT IS CLAIMED IS:

1. A paclitaxel injection formulation comprising: paclitaxel 30mg, povidone 80mg, oxyethylene sorbitol oleate 0.5 to 2.0ml, $(oxyethylene\ glycol)_{15-20}$ fatty acid monoester 0.5 to 2.0ml, polyethylene glycol 1.0 ml, and anhydrous alcohol 2.0ml, the oxyethylene sorbitol oleate being selected from the group consisting of $(oxyethylene)_{60}$ sorbitol tetraoleate and $(oxyethylene)_{45}$ sorbitol trioleate.

2. The paclitaxel injection formulation of claim 1, wherein the oxyethylene glycol fatty acid monoester is selected from the group consisting of oleic acid monoester, 12-hydroxy stearic acid monoester and ricinoleic acid monoester.

3. The paclitaxel injection formulation of claim 1, wherein the number of ethylene oxide addition moles of oxyethylene glycol fatty acid monoester is in the range of 15 to 20.

4. The paclitaxel injection formulation of claim 1, wherein the anhydrous alcohol is selected from the group consisting of anhydrous ethanol, anhydrous isopropyl alcohol, anhydrous n-propyl alcohol and t-butyl alcohol.

ABSTRACT OF THE DISCLOSURE

Disclosed herein is an improved, stable injection paclitaxel formulation. The formulation comprises polyoxyethylene sorbitol oleic polyester as a main solubilizer, and appears to have less toxicity and greater stability compared to polyethoxylated castor oil-containing formulation which is clinically used all over the world.

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Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

AN IMPROVED STABLE INJECTION FORMULATION CONTAINING PACLITAXEL

the specification of which

(check one)

☒ is attached hereto.

☐ was filed on _____ as

Application Serial No. _____

and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
99-9928 (Number)	Korea (Country)	23/03/1999 (Day/Month/Year Filed)	☒ Yes	☐ No
(Number)	(Country)	(Day/Month/Year Filed)	☐ Yes	☐ No
(Number)	(Country)	(Day/Month/Year Filed)	☐ Yes	☐ No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (*list name and registration number*)

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(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
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